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10/593,831	09/22/2006	Toshihiro Akaike	69719.000003	3234

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EXAMINER	
LONG, SCOTT	

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1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/593,831	AKAIKE ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *20 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-9 and 11-20* is/are pending in the application.

4a) Of the above claim(s) *2 and 11-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-9,19 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner acknowledges receipt of Applicant's Remarks and Claim amendments, filed on 20 July 2009.

Election/Restrictions

In his Response to Restriction Requirement (filed 2/2/2009), the applicant explicitly elected, without traverse Group I (claims 1 and 3-10) directed to a method of growing pluripotent stem comprising cultured on surfaces coated with adhesion molecules. Because the applicant explicitly elected without traverse, the restriction was made final, in the action filed 3/18/2009.

Furthermore, the restriction requirement (filed 1/5/2009) was based upon the claims filed 9/22/2006, in which claim 2 was an independent claim directed to a method distinct from the method of claim 1. This was a proper restriction.

To reserve the right to petition, the election must be made with traverse. No traversal was made at the time of election.

In his remarks, filed 7/20/2009, the applicant has requested that the examiner examine claims 2 and 11-18 with claims 1, 3-9 and 19-20. As the examiner has concluded that the original restriction was proper and no traversal was provided with the applicant's election, the applicant's request for examination of claims 2 and 11-18 is denied.

Claim Status

Claims 1, 3-9 and 11-20 are pending. However, claims 2 and 11-18 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 1, 3-9 and 19-20 are under current examination.

Specification

The objected to the specification because of because of an embedded hyperlink and/or other form of browser-executable code is withdrawn in response to the applicant's arguments.

Priority

This application claims benefit as a 371 of a National Stage of PCT/JP05/06006, filed 23 March 2005. This application claims benefit as a foreign application JAPAN 2004-085393, filed 3/23/2004. The instant application has been granted the benefit date, 1 April 2004, from foreign application JAPAN 2004-085393, filed 3/23/2004.

RESPONSE TO ARGUMENTS

35 USC § 112, 2nd

The rejection of claims 3 and 8-10 under 35 USC 112, 2nd paragraph is withdrawn in response to the applicant's claim amendments. The applicant has amended the claims such that the pending claims no longer depend from claim 2. Therefore, the examiner hereby withdraws the rejection of claims 3 and 8-10 under 35 USC 112, 2nd paragraph.

35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Amit

The rejection of claim 10 under 35 U.S.C. 102(b) as being anticipated by Amit et al. (Developmental Biology, 2000; 227: 271-278) is withdrawn in response to the applicant's claim amendments. The applicant has cancelled claim 10. Therefore, this rejection is moot. Therefore, the examiner hereby withdraws the rejection of claim 10 under 35 U.S.C. 102(b) as being anticipated by Amit et al. (Developmental Biology, 2000; 227: 271-278).

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Nagaoka

Claims 1 and 3-9 remain rejected under 35 U.S.C. 103(a) as being obvious over Nagaoka et al (Biotechnology Letters, 2002; 24: 1857-1862) [known hereinafter as Nagaoka1] and as evidenced by Nagaoka et al. (Cell Structure and Function, 2003; 28(4): 327, IP-53) [known hereinafter as Nagaoka2] for the reasons of record and the comments below.

The applicant's arguments have been fully considered but are unpersuasive.

The applicant has amended the preamble of claim 1, changing the word, "growing" to the phrase, "augmenting the proliferation potency of."

The applicant argues "Nagaoka 1 and 2 do not teach pluripotent stem cells." The applicant argues that the F9 teratocarcinoma cells of Nagaoka do not qualify as pluripotent stem cells because "differentiation of F9 cells is limited to endodermal cells." The examiner points out that the instant specification teaches "'Pluripotent stem cells' are defined as cells capable of prolonged or virtually indefinite proliferation *in vitro* while retaining their undifferentiated state, exhibiting normal karyotype (chromosomes) and

having the capacity to differentiate into all cell types of the three germ layers (ectoderm, mesoderm and endoderm) under the appropriate conditions." (page 2, lines 29-35). Nicolas et al, (Ann. Microbiol. Paris., 126: 3-22, 1975) teach F9 embryonal carcinoma cells have normal karyotype and can form all three germ layers. Therefore, according to the definition of pluripotent stem cells provided by the instant specification, F9 embryonal carcinoma cells can be considered pluripotent stem cells because they are cells that have a normal karyotype and can form all three germ layers and are capable of proliferation in vitro while retaining their undifferentiated state. Therefore, the applicant's argument is unpersuasive.

The applicant further argues that the cited references do not teach "augmenting the proliferation potency of pluripotent stem cells" (Remarks, page 6, section B). The examiner notes that the phrase, "augmenting the proliferation potency of pluripotent stem cells," is in the preamble of claim 1. The method steps of claim 1 have not been amended. Nagaoka teaches the active method steps of the instant claims. Therefore, the preamble would seem to be an intrinsic characteristic of practicing the active steps. Furthermore, the specification does not provide a limiting definition of the phrase, "augmenting the proliferation potency of pluripotent stem cells." Therefore, the examiner is broadly interpreting this language to be satisfied by the teachings of Nagaoka. Accordingly, the examiner finds the applicant's argument unpersuasive.

Therefore, the examiner hereby maintains the rejection of claims 1 and 3-9 remain rejected under 35 U.S.C. 103(a) as being obvious over Nagaoka et al.

The examiner reiterates the pending rejection:

Claims 1 and 3-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Nagaoka et al (Biotechnology Letters, 2002; 24: 1857-1862) [known hereinafter as Nagaoka1] and as evidenced by Nagaoka et al. (Cell Structure and Function, 2003; 28(4): 327, IP-53) [known hereinafter as Nagaoka2].

Claim 1 is directed to a method for augmenting the proliferation potency of pluripotent stem cells, comprising growing said pluripotent stem cells in a dispersed state while maintaining their undifferentiated state and pluripotency, in a liquid medium and culturing vessel including immobilize or coated on a substrate solid phase surface a molecule which is adhesive to said pluripotent stem cells, without using feeder cells. Nagaoka1 teach growing F9 teratocarcinoma cells in a liquid medium and in a culturing vessel having a E-cadherin-IgG Fc coated surface (page 1860, col.1). F9 carcinoma teratocarcinoma cells are an undifferentiated cell line derived from a mouse embryonal carcinoma that is frequently used as a model for studying differentiation and pluripotency. In Nagaoka1, the F9 cells were used as a control and were not the primary subject of interest in the Nagaoka1. However, Nagaoka2 indicates that F9 mouse teratocarcinoma-derived embryonal carcinoma cells cultured on immobilized E-cad-Fc [fusion protein of E-cadherin extracellular domain and Immunoglobulin G (IgG) Fc region] remained undifferentiated. No feeder cells were used in either reference. Since the F9 cells in Nagaoka1 were cultured under identical conditions as in Nagaoka2, the examiner asserts that Nagaoka1 inherently satisfies the limitations of claim 1. F9 embryonal carcinoma cells have normal karyotype and can form all three germ layers. The instant specification teaches "'Pluripotent stem cells' are defined as

cells capable of prolonged or virtually indefinite proliferation in vitro while retaining their undifferentiated state, exhibiting normal karyotype (chromosomes) and having the capacity to differentiate into all cell types of the three germ layers (ectoderm, mesoderm and endoderm) under the appropriate conditions." (page 2, lines 29-35). Therefore, according to the definition of pluripotent stem cells provided by the instant specification, F9 embryonal carcinoma cells can be considered pluripotent stem cells because they are cells that have a normal karyotype and can form all three germ layers and are capable of proliferation in vitro while retaining their undifferentiated state.

Claim 3 is directed to the method of claim 1, wherein the molecule which is adhesive to said pluripotent stem cells is either a molecule that is expressed by said pluripotent stem cells or a molecule that is structurally homologous with said molecule and has homophilic binding ability with said pluripotent stem cells. Nagaoka1 describes the E-cad-Fc as creating a homophilic interaction of E-cadherins (abstract).

Claim 4 is directed to the method of claim 3, wherein the molecule which is adhesive to said pluripotent stem cells is a molecule belonging to the cadherin family. The molecule, E-cadherin, is a part of the cadherin family.

Claim 5 is directed to the method of claim 4, wherein said molecule belonging to the cadherin family is E-cadherin, or a molecule which has structural homology with said molecule, which comprises the EC1 domain and one or more domains from among the EC2 domain, EC3 domain, EC4 domain and EC5 domain and which has homophilic binding ability with said pluripotent stem cells. The molecule, E-cadherin, is a part of

the cadherin family. Nagaoka1 describes the E-cad-Fc as creating a homophilic interaction of E-cadherins (abstract).

Claim 6 is directed to the method of claim 5, wherein said E-cadherin is obtained from a mammal. The extracellular domain of E-cadherin used in the fusion protein is from mouse E-cadherin (Nagaoka1, Figure 1, page 1858).

Claim 7 is directed to the method of claim 6, wherein said E-cadherin is obtained from a human or mouse. The extracellular domain of E-cadherin used in the fusion protein is from mouse E-cadherin (Nagaoka1, Figure 1, page 1858).

Claim 8 is directed to the method of claim 1, wherein the molecule which is adhesive to said pluripotent stem cells is fused with an immunoglobulin Fc region and is immobilized on said substrate solid phase surface via said Fc region. Nagaoka1 teach a fusion protein comprising E-cadherin extracellular domain and Immunoglobulin G (IgG) Fc region. Nagaoka1 teach "we have applied an engineered protein of E-cadherin extracellular domain and immunoglobulin G (IgG) Fc region because Fc region has the potentiality to stably adsorb to a plastic surface such as polystyrene and dimerize via the hinge region." (page 1857, col.2).

Claim 9 is directed to the method of claim 1, wherein said pluripotent stem cells are mammalian embryonic stem cells (ES cells) or embryonic germ cells (EG cells). The specification indicates "'Pluripotent stem cells' are defined as cells capable of prolonged or virtually indefinite proliferation in vitro while retaining their undifferentiated state, exhibiting normal karyotype (chromosomes) and having the capacity to differentiate into all cell types of the three germ layers (ectoderm, mesoderm and

endoderm) under the appropriate conditions." (page 2, lines 29-35). The F9 mouse teratocarcinoma-derived embryonal carcinoma cells of Nakaoka have a polyoma-based plasmid that persists as an episome, but have a normal karyotype. These cells are capable of differentiation into virtually all cell types of the body. Therefore, the examiner concludes the F9 cells of Nakaoka satisfy the limitations of claim 9.

Accordingly, Nagaoka et al. anticipated the instant claims.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 19-20 are rejected under 35 U.S.C. 103(a) as being obvious over Nagaoka et al (Biotechnology Letters, 2002; 24: 1857-1862) [known hereinafter as Nagaoka1] in view of Nagaoka et al. (Cell Structure and Function, 2003; 28(4): 327, IP-53) [known hereinafter as Nagaoka2] as applied to claim 1 above.

Claim 19 is directed to the method of claim 1, wherein the molecule which is adhesive to said pluripotent stem cells is E-cadherin obtained from a human or mouse and said pluripotent stem cells are mammalian embryonic stem cells (ES cells). Nagaoka teach the method of claim 1 as described above in the 35 USC 102(b) rejection. Nagaoka do not explicitly teach culturing embryonic stem cells. However, Nagaoka2 teach that the E-cadherin-Fc fusion protein could be used to study embryonic development. This is suggestive of culturing mammalian embryonic stem cells in the method of claim 1, as culturing embryonic stem cells would provide the suitable material for studies of mammalian development. As the cells used in the Nagaoka are murine cells, therefore mammalian embryonic stem cells are suggested. Furthermore, Nagaoka teaches that the E-cadherin domain of the E-cad-Fc fusion protein is from a mouse (Fig.1)

Claim 20 is directed to the method of claim 19, wherein the E-cadherin is fused with an immunoglobulin region and is immobilized on said substrate solid surface via said Fc region. Nagaoka teaches that the Fc region has the potentiality to stably adsorb to a plastic surface (page 1857, col.2).

It would have been obvious to the person of ordinary skill in the art at the time of the invention was made to culture mammalian embryonic stem cells using the system of Nagaoka.

The person of ordinary skill in the art would have been motivated to make that modification to culture mammalian embryonic stem cells using the system of Nagaoka because Nagaoka2 suggests that the E-cadherin-Fc fusion protein could be used to study embryonic development and a suitable material for studies of mammalian development would be mammalian embryonic stem cells.

An artisan would have expected success, because Nagaoka demonstrates a method of growing pluripotent cells such as F9 mouse teratocarcinoma-derived embryonal carcinoma cells are known to be useful as a model of embryonic development.

Therefore the method as taught by Nagaoka et al would have been *prima facie* obvious over the method of the instant application.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Scott Long/
Patent Examiner, Art Unit 1633